9-9-09

HARNESS DICKEY

2 September 2009

Food and Drug Administration
Division of Dockets Management (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: FDA-2008-E-0113

Determination of Regulatory Review Period for Purposes of Patent Extension;
LETAIRIS (74 Fed. Reg. 6635-36)

Dear Sirs:

Gilead Sciences, Inc. ("Gilead"; formerly Myogen, Inc.) is Sponsor of a New Drug Application ("NDA") filed on 18 December 2006 for drug LETAIRIS, which was approved on 15 June 2007. Harness, Dickey and Pierce, P.L.C. ("HDP"), as agent for Gilead is authorized to communicate with the FDA on matters bearing on determination of regulatory review period for LETAIRIS (ambrisentan) under 35 U.S.C. §156(g)(1)(B), as required to file Patent Term Extension Applications.

FDA Finding

FDA determined on 10 February 2009 that the investigational new drug ("IND") application (IND #63,915) effective date for LETAIRIS is 3 May 2002, a date earlier than determined by Gilead.

Gilead Concurrence

Gilead concurs with FDA finding of an earlier effective IND date. On behalf of Gilead, HDP submits comments, along with exhibits herewith, supporting FDA determinations as to LETAIRIS regulatory review period, as published in Federal Register Vol. 74, No. 26, pp. 6635-36 (Exhibit A). References herein to "Gilead" include, as appropriate, activities conducted by predecessor Myogen, Inc. ("Myogen").

Analysis

FDA determined on 10 February 2009 that the investigational new drug ("IND") application (IND #63,915) effective date for LETAIRIS is 3 May 2002 because a previous IND, (IND #63,412) related to ambrisentan, was removed from full clinical hold on that day. A testing phase begins on IND effective date and ends on the date the approval-review phase begins. Typically, an IND becomes effective 30 days after FDA receives the IND (21 C.F.R. §312.40 (b)(1)), but it can become effective before the 30-day period with an earlier notification by FDA that the clinical investigations described in the IND may begin (21 C.F.R. §312.40 (b)(2)). If an IND was placed on clinical hold, the effective date is the date when the FDA informs the sponsor that all clinical hold issues have been resolved (53 Fed. Reg. 7298 (7 March 1988)).

Where multiple IND's have been filed leading to approval of a drug product, multiple IND effective dates could result from such filings, and the first-filed IND can be a basis for determining a testing phase, see 53 Fed. Reg. 7298 (7 March 1988):

> "Where multiple IND's are in effect, the agency will consider the testing phase to have begun when the first IND for the approved human drug product became effective."

To get an earlier IND effective date, however, some nexus between the earlier-filed IND and the approval of the drug product is likely necessary, see 53 Fed. Reg. 7298 (7 March 1988):

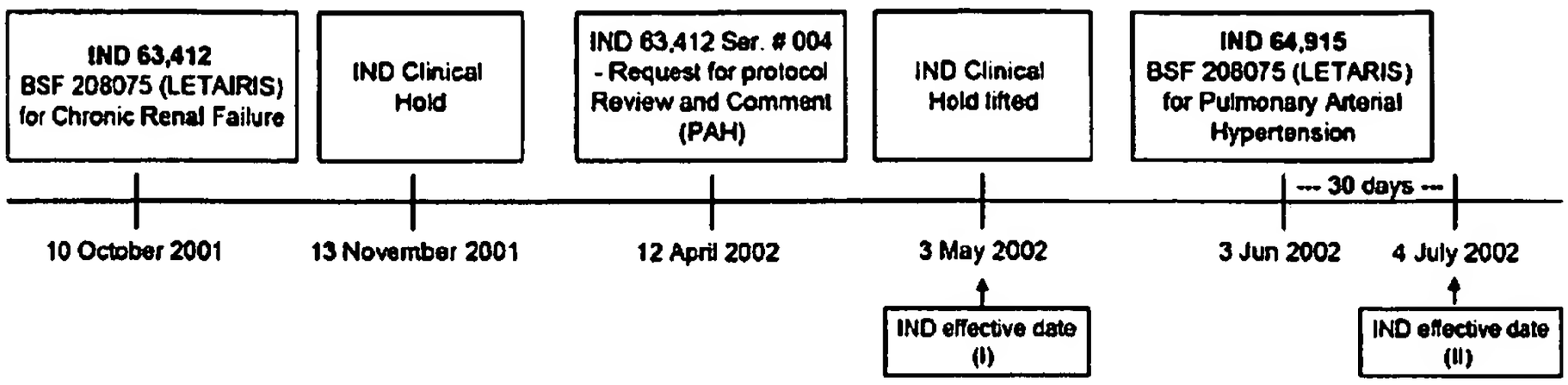
> "While the drug's dosage form and strength during the IND phase need not be identical to that of the approved drug product, the information from the IND studies must have been material to the approval of the drug product."

In sum, a testing phase can be counted from the effective date of an earlier-filed IND if the earlier-filed IND was material to the approval of the drug product.

Based upon search and review of documents and communications between Sponsor Gilead and FDA, HDP and Gilead have reached the same conclusion as FDA that the IND effective date for LETAIRIS is the date when the previous IND (i.e., IND #63,412) was removed from full clinical hold (i.e., 3 May 2002).

Gilead submitted two IND's in connection with clinical study of the active compound, BSF 208075 (ambrisentan). See LETAIRIS IND timeline below and LETAIRIS test phase chronology (Exhibit B).

LETAIRIS IND TIMELINE



A first IND (IND #63,412) was submitted on 10 October 2001 to study BSF 208075 for treatment of chronic renal failure (CRF). The first IND, however, was put on hold on 13 November 2001 because of toxicity issues, but the clinical hold was lifted on 3 May 2002 after submission of a complete response by the Sponsor (Myogen). A second IND (IND #64,915) was filed on 3 June 2002 to study BSF 208075 for treatment of pulmonary arterial hypertension (PAH). Therefore, LETAIRIS has two candidates for IND effective date: (a) the date clinical hold for the first IND was lifted (i.e., 3 May 2002) and (b) 30 days after IND 64,915 submission (i.e., 4 July 2002).

Gilead believes that research activities before IND effective date (a) are material to the approval of the drug product, and accordingly IND effective date (a) should be basis for start of testing phase of LETAIRIS. IND #63,412 (submitted 10 October 2001) was intended to conduct clinical research on BSF 208075 for treatment of CRF. However, the FDA decided to place the IND on hold because of concerns as to potential toxicity of BSF 208075, i.e., testicular atrophy. Gilead had diligently conducted discussions with the FDA relating to a follow-up study for toxicity evaluation and research results until 3 May 2002 when the clinical hold was lifted. The toxicity issue discussed was common to all indications of BSF 208075 including PAH, inasmuch as Dr. Lipicky (FDA Director, Division of cardio-renal

drug products) stated in 9 November 2001 telecon that "the same toxicology problem with the testes exists no matter what the indication." Therefore, research activities and discussions prior to the hold-lifting date (i.e., 3 May 2002) were material for approval of the drug product.

Furthermore, Gilead discussed clinical study strategy and protocol for treatment of PAH during pendency of IND #63,412 for CRF indication. After the FDA clinical hold became effective, Gilead began to discuss possibility of studying other indications including PAH on 14 November 2001 (see summary of 14 November 2001 teleconference, Exhibit B) and then maintained continuous discussions with the FDA on both CRF and PAH research protocols until the clinical hold was lifted. After several rounds of discussion, Gilead submitted "IND #63,412, Serial #004 - Request for Protocol Review and Comment (PAH)" on 12 April 2002, which was designed to investigate PAH indication. Even though IND #63,412 was initially intended to study CRF indication, FDA and Sponsor (Myogen) discussed both CRF and PAH indications substantially under IND #63,412. Thus, such research activities and discussions prior to the hold-lifting date related directly to the approval of LETAIRIS since both IND #63,412 and IND #64,915 were involved in study for treatment of PAH.

Two major topics discussed during IND #63,412 were (1) toxicity issues of BSF 208075 which needed to be resolved to study PAH indication and (2) study protocol for PAH clinical research. Both topics were material and necessary to move forward with IND #64,915 for PAH research. Therefore, IND effective date for LETAIRIS should be 3 May 2001 when the clinical hold for IND #63,412 was lifted.

According to Regulations.gov (a web-based database on Federal regulations and documents), as of deadline of 13 April 2009, no written or electronic comment has been submitted by any other party that any of the dates as published in the Federal Register Notice (Exhibit A) is incorrect as to FDA determination of the regulatory review period of LETAIRIS. See the docket of FDA-2008-E-0113 (Exhibit C) retrieved from Regulations.gov

on 24 August 2009. Gilead submits the comments above in support of the FDA's determination on LETAIRIS regulatory review period published in the Federal Register Notice.

Sincerely,

By: J. Timothy Keane

J. Timothy Keane
Principal
HARNESS, DICKEY & PIERCE, P.L.C.
7700 Bonhomme, Suite 400
St. Louis, Missouri 63105
314-726-7500 (telephone)
314-726-7501 (facsimile)

Attachments

Exhibit A – Federal Register Vol. 74, No. 26, pp. 6635-36

Exhibit B – LETAIRIS test phase chronology

Exhibit C – Docket record of FDA-2008-E-0113, as of 24 August 2009, retrieved from Regulations.gov

C.c.: Mary C. Till, U.S. Patent Office
Madhavi Chander, Gilead Sciences
Paul D. Yasger, Abbott Labs